LAMOTRIGINE - lamotrigine tablet
McKesson Packaging Services Business Unit of McKesson Corporation

Rx only
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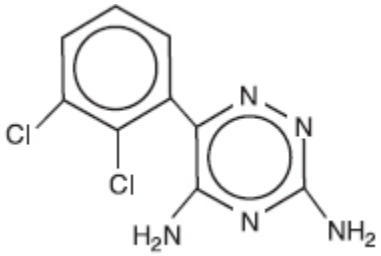
SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMOTRIGINE. THE INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED STEVENS-JOHNSON SYNDROME, IS APPROXIMATELY 0.8% (8 PER 1,000) IN PEDIATRIC PATIENTS (AGE < 16 YEARS) RECEIVING LAMOTRIGINE AS ADJUNCTIVE THERAPY FOR EPILEPSY AND 0.3% (3 PER 1,000) IN ADULTS ON ADJUNCTIVE THERAPY FOR EPILEPSY. IN CLINICAL TRIALS OF BIPOLAR AND OTHER MOOD DISORDERS, THE RATE OF SERIOUS RASH WAS 0.08% (0.8 PER 1,000) IN ADULT PATIENTS RECEIVING LAMOTRIGINE AS INITIAL MONOTHERAPY AND 0.13% (1.3 PER 1,000) IN ADULT PATIENTS RECEIVING LAMOTRIGINE AS ADJUNCTIVE THERAPY. IN A PROSPECTIVELY FOLLOWED COHORT OF 1,983 PEDIATRIC PATIENTS WITH EPILEPSY TAKING ADJUNCTIVE LAMOTRIGINE, THERE WAS 1 RASH-RELATED DEATH. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED IN ADULT AND PEDIATRIC PATIENTS, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.
OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMOTRIGINE. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY (1) CO-ADMINISTRATION OF LAMOTRIGINE WITH VALPROATE (INCLUDES VALPROIC ACID AND DIVALPROEX SODIUM), (2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMOTRIGINE, OR (3) EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMOTRIGINE. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.
NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMOTRIGINE HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (e.g., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.
ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMOTRIGINE, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMOTRIGINE SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUGRELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

DESCRIPTION

Lamotrigine, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its molecular formula is C9H7N5Cl2, and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder and has a pKa of 5.7. Lamotrigine is slightly soluble in methanol. The structural formula is:



Lamotrigine tablets are supplied for oral administration as 25 mg, 100 mg, 150 mg, and 200 mg tablets. Each tablet contains the labeled amount of lamotrigine and the following inactive ingredients: hydroxypropyl cellulose; L- hydroxypropyl cellulose; magnesium stearate; mannitol; powdered cellulose; talc; and ferric oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for

antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state.The relevance of these models to human epilepsy, however, is not known.
One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. *In vitro* pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate). The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder have not been established.

Pharmacological Properties:
Although the relevance for human use is unknown, the following data characterize the performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect on the serotonin 5-HT3 receptor (IC50 = 18 µM). It does not exhibit high affinity binding (IC50 > 100 µM) to the following neurotransmitter receptors: adenosine A1 and A2; adrenergic #$_1$, #$_2$, and B; dopamine D1 and D2; #-aminobutyric acid (GABA) A and B; histamine H1; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT2. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC50 = 145 µM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin (IC50 > 200 µM) when tested in rat synaptosomes and/or human platelets *in vitro*.

Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:
Lamotrigine did not inhibit N-methyl daspartate (NMDA)-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC50 for lamotrigine effects on NMDA-induced currents (in the presence of 3 µM of glycine) in cultured hippocampal neurons exceeded 100 µM.

Folate Metabolism:
In vitro, lamotrigine was shown to be an inhibitor of dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis (see **PRECAUTIONS**: **Pregnancy**). Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Accumulation in Kidneys:
Lamotrigine was found to accumulate in the kidney of the male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to #-2 microglobulin, a species-and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding:
Lamotrigine binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Cardiovascular:
In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (< 0.6% of lamotrigine dose) have been found in human urine (see **Drug Disposition**). However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease).

Pharmacokinetics and Drug Metabolism:
The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric patients and healthy normal volunteers are summarized in Tables 1 and 2.

Table 1. Mean* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients With Epilepsy

Adult Study Population	Number of Subjects	Tmax: Time of Maximum Plasma Concentration (h)	t1/2: Elimination Half-life (h)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:				
Single-dose Lamotrigine	179	2.2	32.8	0.44

		(0.25 to 12.0)	(14.0 to 103.0)	(0.12 to 1.10)
Multiple-dose Lamotrigine	36	1.7 (0.5 to 4.0)	25.4 (11.6 to 61.6)	0.58 (0.24 to 1.15)
Healthy volunteers taking valproate:				
Single-dose Lamotrigine	6	1.8 (1.0 to 4.0)	48.3 (31.5 to 88.6)	0.30 (0.14 to 0.42)
Multiple-dose Lamotrigine	18	1.9 (0.5 to 3.5)	70.3 (41.9 to 113.5	0.18 (0.12 to 0.33)
Patients with epilepsy taking valproate only:				
Single-dose Lamotrigine	4	4.8 (1.8 to 8.4)	58.8 (30.5 to 88.8)	0.28 (0.16 to 0.40)
Patients with epilepsy taking carbamazepine,phenytoin, phenobarbital, or primidone† plus valproate:				
Single-dose Lamotrigine	25	3.8 (1.0 to 10.0)	27.2 (11.2 to 51.6)	0.53 (0.27 to 1.04)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone†:				
Single-dose Lamotrigine	24	2.3 (0.5 to 5.0)	14.4 (6.4 to 30.4)	1.10 (0.51 to 2.22)
Multiple-dose Lamotrigine	17	2.0 (0.75 to 5.93)	12.6 (7.5 to 23.1)	1.21 (0.66 to 1.82)

*****The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half life and Cl/F and between 30% and 70% for Tmax. The overall mean values were calculated from individual study means that were weighted based on the number of volunteers/patients in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/patient values across studies.

†Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine.Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see **CLINICAL PHARMACOLOGY**, **Drug Interactions** and **PRECAUTIONS**, **Drug Interactions**).

Absorption:
Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration.

Distribution:
Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding:
Data from *in vitro* studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

Drug Disposition:
Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of 14C-lamotrigine (15 µCi) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucurodine (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Drug Interactions:
The apparent clearance of lamotrigine is affected by the co-administration of certain medications. Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine.

Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**: **Drug Interactions**). Most clinical experience is derived from patients taking these AEDs.

Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see **PRECAUTIONS**: **Drug Interactions**).

Valproate decreases the apparent clearance of lamotrigine (i.e., more than doubles the elimination half-life of lamotrigine),whether given with or without carbamazepine, phenytoin, phenobarbital, or primidone. Accordingly, if lamotrigine is to be administered to a patient receiving valproate, lamotrigine must be given at a reduced dosage, no more than half the dose used in patients not receiving valproate, even in the presence of drugs that increase the apparent clearance of lamotrigine (see **DOSAGE AND ADMINISTRATION**and **PRECAUTIONS**: **Drug Interactions**).

The following drugs were shown not to increase the apparent clearance of lamotrigine: felbamate, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and topiramate. Zonisamide does not appear to change the pharmacokinetic profile of lamotrigine (see **PRECAUTIONS**: **Drug Interactions**).

In vitro inhibition experiments indicated that the formation of the primary metabolite of lamotrigine, the 2-N-glucuronide, was not significantly affected by co-incubation with clozapine, fluoxetine, phenelzine, risperidone, sertraline, or trazodone, and was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. In addition, bufuralol metabolism data from human liver microsomes suggested that lamotrigine does not inhibit the metabolism of drugs eliminated predominantly by CYP2D6.

Lamotrigine has no effects on the pharmacokinetics of lithium (see **PRECAUTIONS**: **Drug Interactions**).

The pharmacokinetics of lamotrigine were not changed by co-administration of bupropion (see **PRECAUTIONS**: **Drug Interactions**).

Co-administration of olanzapine did not have a clinically relevant effect on lamotrigine pharmacokinetics (see **PRECAUTIONS**: **Drug Interactions**).

Enzyme Induction:
The effects of lamotrigine on the induction of specific families of mixed-function oxidase isozymes have not been systematically evaluated.

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in t1/2 and a 37% increase in Cl/F at steady state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that selfinduction by lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

Dose Proportionality:
In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice daily.

Elimination:
(See Table 1.)

Special Populations:
Patients With Renal Insufficiency:

Twelve volunteers with chronic renal failure (mean creatinine clearance = 13 mL/min; range = 6 to 23) and another 6 individuals undergoing hemodialysis were each given a single 100 mg dose of lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session.

Hepatic Disease:

The pharmacokinetics of lamotrigine following a single 100 mg dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic dysfunction (Child-Pugh Classification system) and compared with 12 subjects without hepatic impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with ascites (n = 5). The mean apparent clearance of lamotrigine in patients with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment was 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared to 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-life of lamotrigine in patients with mild, moderate, severe without ascites, and severe with ascites liver impairment was 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared to 33 ± 7 hours in healthy controls (for dosing guidelines, see **DOSAGE AND ADMINISTRATION**: **Patient With Hepatic Impairment**).

Age:

Pediatric Patient:
The pharmacokinetics of lamotrigine following a single 2 mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients aged 10 months to 5.9 years and n = 26 for patients aged 5 to 11 years). Forty-three patients received concomitant therapy with other AEDs and 12 patients received lamotrigine as monotherapy. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 2.

Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing more than 30 kg being administered the same AEDs (see **DOSAGE AND ADMINISTRATION**). These analyses also revealed that, after accounting for body weight, lamotrigine clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in adults were found to have similar effects in children.

Table 2. Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy

Pediatric Study Population	Number of Subjects	Tmax (h)	t1/2 (h)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	10	3.0 (1.0 - 5.9)	7.7 (5.7 - 11.4)	3.62 (2.44 - 5.28)
Patients taking antiepileptic drugs (AEDs) with no known effect on the apparent clearance of lamotrigine	7	5.2 (2.9 - 6.1)	19.0 (12.9 - 27.1)	1.2 (0.75 - 2.42)
Patients taking valproate only	8	2.9 (1.0 to 6.0)	44.9 (29.5 to 52.5)	0.47 (0.23 to 0.77)
Ages 5-11 years				
Patients taking carbamazepine, phenytoin,	7	1.6	7.0	2.54

phenobarbital, or primidone*		(1.0 - 3.0)	(3.8 - 9.8)	(1.35 - 5.58)
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* plus valproate	8	3.3 (1.0 - 6.4)	19.1 (7.0 - 31.2)	0.89 (0.39 - 1.93)
Patients taking valproate only†	3	4.5 (3.0 - 6.0)	65.8 (50.7 - 73.7)	0.24 (0.21 - 0.26)
Ages 13-18 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	11	‡	‡	1.3
Patients taking carbamazpine, phenytoin, phenobarbital, or primidone* plus valproate	8	‡	‡	0.5
Patients taking valproate only	4	‡	‡	0.3

*****Carbamazpine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine.Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see **CLINICAL PHARMACOLOGY**: **Drug Interactions**and **PRECAUTIONS**: **Drug Interactions**)
†Two subjects were included in the calculation for mean Tmax.
‡Parameter not estimated.

Elderly:
The pharmacokinetics of lamotrigine following a single 150 mg dose of lamotrigine tablets were evaluated in12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min, range = 33 to 108 mL/min). The mean half-life of lamotrigine in these subjects was 31.2 hours (range, 24.5 to 43.4 hours), and the mean clearance was 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/ kg).

Gender:
The clearance of lamotrigine is not affected by gender. However, during dose escalation of lamotrigine in one clinical trial in patients with epilepsy on a stable dose of valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

Race:
The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

CLINICAL STUDIES

Epilepsy:
The results of controlled clinical trials established the efficacy of lamotrigine as monotherapy in adults with partial onset seizures already receiving treatment with carbamazepine, phenytoin, phenobarbital, or primidone as the single antiepileptic drug (AED), as adjunctive therapy in adults and pediatric patients age 2 to 16 with partial seizures, and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

Monotherapy With Lamotrigine in Adults With Partial Seizures Already Receiving Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single AED:
The effectiveness of monotherapy with lamotrigine was established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The patients experienced at least 4 simple partial, complex partial, and/or secondarily generalized seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or phenytoin monotherapy during baseline.

Lamotrigine (target dose of 500 mg/day) or valproate (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy with lamotrigine or valproate during the next 4 weeks, then continued on monotherapy for an additional 12-week period.

Study endpoints were completion of all weeks of study treatment or meeting an escape criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more severe than seizure types that occur during study treatment, or (4) clinically significant prolongation of generalized-tonic-clonic (GTC) seizures. The primary efficacy variable was the proportion of patients in each treatment group who met escape criteria.

The percentage of patients who met escape criteria was 42% (32/76) in the lamotrigine group and 69% (55/80) in the valproate group. The difference in the percentage of patients meeting escape criteria was statistically significant ($p = 0.0012$) in favor of lamotrigine. No differences in efficacy based on age, sex, or race were detected.

Patients in the control group were intentionally treated with a relatively low dose of valproate; as such, the sole objective of this study was to demonstrate the effectiveness and safety of monotherapy with lamotrigine, and cannot be interpreted to imply the superiority of lamotrigine to an adequate dose of valproate.

Adjunctive Therapy With Lamotrigine in Adults With Partial Seizures:
The effectiveness of lamotrigine as adjunctive therapy (added to other AEDs) was established in 3 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their established AED regimen during baselines that varied between 8 to 12 weeks. In the third, patients were not observed in a prospective baseline. In patients continuing to have at least 4 seizures per month during the baseline, lamotrigine or placebo was then added to theexisting therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of effectiveness. The results given below are for all partial seizures in the intent-to-treat population (all patients who received at least one dose of treatment) in each study, unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline was 6.6 per week for all patients enrolled in efficacy studies.

One study ($n = 216$) was a double-blind, placebo-controlled, parallel trial consisting of a 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. Patients were randomized to receive placebo, a target dose of 300 mg/day of lamotrigine, or a target dose of 500 mg/day of lamotrigine. The median reductions in the frequency of all partial seizures relative to baseline were 8% in patients receiving placebo, 20% in patients receiving 300 mg/day of lamotrigine, and 36% in patients receiving 500 mg/day of lamotrigine. The seizure frequency reduction was statistically significant in the 500 mg/day group compared to the placebo group, but not in the 300 mg/day group.

A second study ($n = 98$) was a double-blind, placebo-controlled, randomized, crossover trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose tapering) separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment periods were analyzed, the median change in seizure frequency was a 25% reduction on lamotrigine compared to placebo ($p < 0.001$).

The third study ($n = 41$) was a double-blind, placebo-controlled, crossover trial consisting of two 12-week treatment periods separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these patients received 150 mg/day of lamotrigine. The 28 other patients had a target dose of 300 mg/day of lamotrigine. The median change in seizure frequency was a 26% reduction on lamotrigine compared to placebo ($p < 0.01$).

No differences in efficacy based on age, sex, or race, as measured by change in seizure frequency, were detected.

Adjunctive Therapy With Lamotrigine in Pediatric Patients with Partial Seizures:
The effectiveness of lamotrigine as adjunctive therapy in pediatric patients with partial seizures was established in a multicenter, double-blind, placebo-controlled trial in 199 patients aged 2 to 16 years ($n = 98$ on lamotrigine, $n = 101$ on placebo). Following an 8-week baseline phase, patients were randomized to 18 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg per day for patients taking valproate (maximum dose, 250 mg/day) and 15 mg/kg per day for patients not taking valproate (maximum dose, 750 mg per day). The primary efficacy endpoint was percentage change from baseline in all partial seizures. For the intent-to-treat population, the median reduction of all partial seizures was36% in patients treated with lamotrigine and 7% on placebo, a difference that was statistically significant ($p < 0.01$).

Adjunctive Therapy With Lamotrigine in Pediatric and Adult Patients With Lennox-Gastaut Syndrome:
The effectiveness of lamotrigine as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, doubleblind, placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on lamotrigine, n = 90 on placebo). Following a 4-week single-blind, placebo phase, patients were randomized to 16 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 3 drugs. Patients were dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg per day for patients taking valproate (maximum dose, 200 mg/day) and 15 mg/kg per day for the patients not taking valproate (maximum dose, 400 mg/day). The primary efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic, major myoclonic, and tonicclonic seizures). For the intent-to-treat population, the median reduction of major motor seizures was 32% in patients treated with lamotrigine and 9% on placebo, a difference that was statistically significant ($p < 0.05$). Drop attacks were significantly reduced by lamotrigine (34%) compared to placebo (9%), as were tonic-clonic seizures (36% reduction versus 10% increase for lamotrigine and placebo, respectively).

Bipolar Disorder:
The effectiveness of lamotrigine in the maintenance treatment of Bipolar I Disorder was established in 2 multicenter, double-blind, placebo-controlled studies in adult patients who met DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current or recent (within 60 days) depressive episode as defined by DSM-IV and Study 2 included patients with a current or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both studies included a cohort of patients (30% of 404 patients in Study 1 and 28% of 171 patients in Study 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).
In both studies, patients were titrated to a target dose of 200 mg of lamotrigine, as add-on therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during an 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label period were receiving 1 or more other psychotropic medications, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine), valproate, or lithium, during titration of lamotrigine. Patients with a CGI-severity score of 3 or less maintained for at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, were randomized to a placebo-controlled, double-blind treatment period for up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or one that was emerging, time to discontinuation for either an adverse event that was judged to be related to Bipolar Disorder, or for lack of efficacy). The mood episode could be depression, mania, hypomania, or a mixed episode.
In Study 1, patients received double-blind monotherapy with lamotrigine, 50 mg/day (n = 50), lamotrigine 200 mg/day (n= 124), lamotrigine 400 mg/day (n = 47), or placebo (n = 121). Lamotrigine (200 and 400 mg/day treatment groups combined) was superior to placebo in delaying the time to occurrence of a mood episode. Separate analyses of the 200 and 400 mg/day dose groups revealed no added benefit from the higher dose. In Study 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was superior to placebo in delaying the time to occurrence of a mood episode. The mean lamotrigine dose was about 211 mg/ day.
Although these studies were not designed to separately evaluate time to the occurrence of depression or mania, a combined analysis for the 2 studies revealed a statistically significant benefit for lamotrigine over placebo in delaying the time to occurrence of both depression and mania, although the finding was more robust for depression.

INDICATIONS AND USAGE

Epilepsy:

Adjunctive Use:
Lamotrigine tablets are indicated as adjunctive therapy for partial seizures and the generalized seizures of Lennox-Gastaut syndrome in adults and pediatric patients (≥ 2 years of age).

Monotherapy Use:
Lamotrigine tablets are indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

Safety and effectiveness of lamotrigine have not been established (1) as initial monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs (see **DOSAGE AND ADMINISTRATION**).

Bipolar Disorder:
Lamotrigine tablets are indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.
The effectiveness of lamotrigine as maintenance treatment was established in 2 placebo-controlled trials of 18 months' duration in patients with Bipolar I Disorder as defined by DSM-IV (see **CLINICAL STUDIES**, **Bipolar Disorder**). The physician who elects to use lamotrigine for periods extending beyond 18 months should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Lamotrigine tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS
SEE BOX WARNING REGARDING THE RISK OF SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATIONOF LAMOTRIGINE. ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMOTRIGINE, IT IS NOT POSSIBLETO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING. ACCORDINGLY,LAMOTRIGINE SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH ISCLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMINGLIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

Serious Rash:

Pediatric Population:
The incidence of serious rash associated with hospitalization and discontinuation of lamotrigine in a prospectively followed cohort of pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983 patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in U.S. and foreign postmarketing experience. There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially lifethreatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared to 0.6% (6 of 952) patients not taking valproate.

Adult Population:
Serious rash associated with hospitalization and discontinuation of lamotrigine occurred in 0.3% (11 of 3,348) of adult patients who received lamotrigine in premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received lamotrigine as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received lamotrigine as adjunctive therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate.

Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, hematologic, and hepatologic abnormalities.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered lamotrigine with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered lamotrigine in the absence of valproate were hospitalized.

Other examples of serious and potentially life-threatening rash that did not lead to hospitalization also occurred in premarketing development. Among these, 1 case was reported to be Stevens-Johnson-like.

Hypersensitivity Reactions:
Hypersensitivity reactions, some fatal or life threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patients should be evaluated immediately. Lamotrigine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.
Prior to initiation of treatment with lamotrigine, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

Acute Multiorgan Failure:
Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving lamotrigine. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received lamotrigine in clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these

deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial cause.
Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after lamotrigine was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with lamotrigine was discontinued.

Blood Dyscrasias:
There have been reports of blood dyscrasias that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

Withdrawal Seizures:
As with other AEDs, lamotrigine should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid withdrawal, the dose of lamotrigine should be tapered over a period of at least 2 weeks (see **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

Concomitant Use With Oral Contraceptives:
Some estrogen-containing oral contraceptives have been shown to decreaseserum concentrations of lamotrigine (see **PRECAUTIONS**: **Drug Interactions**). **Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking lamotrigine (see DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral Contraceptives: Adjustments to the Maintenance Dose of Lamotrigine).** During the week of inactive hormone preparation (“pill-free” week) of oral contraceptive therapy, plasma levels are expected to rise, as much as doubling by the end of the week. Adverse events consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

Dermatological Events:
(see BOX WARNING, WARNINGS):
Serious rashes associated with hospitalization and discontinuation of lamotrigine have been reported. Rare deaths have been reported, but their numbers are too few to permit a precise estimate of the rate. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of lamotrigine with valproate, (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. However, cases have been reported in the absence of these factors.
In epilepsy clinical trials, approximately 10% of all patients exposed to lamotrigine developed a rash. In the Bipolar Disorder clinical trials, 14% of patients exposed to lamotrigine developed a rash. Rashes associated with lamotrigine do not appear to have unique identifying features. Typically, rash occurs in the first 2 to 8 weeks following treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.
Although most rashes resolved even with continuation of treatment with lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life threatening. **ACCORDINGLY, LAMOTRIGINE SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.**
It is recommended that lamotrigine not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued lamotrigine, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the previous dose, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued lamotrigine for a period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of lamotrigine is affected by other concomitant medications (see **CLINICAL PHARMACOLOGY**: **Pharmacokinetics and Drug Metabolism**, and **DOSAGE AND ADMINISTRATION**).

Use in Patients With Epilepsy:

Sudden Unexplained Death in Epilepsy (SUDEP):
During the premarketing development of lamotrigine, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is

within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving lamotrigine (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for lamotrigine, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving lamotrigine and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving lamotrigine and those receiving another antiepileptic drug that underwent clinical testing in a similar population at about the same time. Importantly, that drug is chemically unrelated to lamotrigine. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

Status Epilepticus:
Valid estimates of the incidence of treatment emergent status epilepticus among patients treated with lamotrigine are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 7 of 2,343 adult patients had episodes that could unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Use in Patients With Bipolar Disorder:

Acute Treatment of Mood Episodes:
Safety and effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.

Children and Adolescents (Less Than 18 Years of Age):
Treatment with antidepressants is associated with an increased risk of suicidal thinking and behavior in children and adolescents with major depressive disorder and other psychiatric disorders. It is not known whether lamotrigine is associated with a similar risk in this population (see **PRECAUTIONS**: **Clinical Worsening and Suicide Risk Associated with Bipolar Disorder**).

Safety and effectiveness of lamotrigine in patients below the age of 18 years with mood disorders have not been established.

Clinical Worsening and Suicide Risk Associated with Bipolar Disorder:
Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and /or the emergence of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/ behavior especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Prescriptions for lamotrigine tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Overdoses have been reported for lamotrigine, some of which have been fatal (see **OVERDOSAGE**).

Addition of Lamotrigine to a Multidrug Regimen That Includes Valproate (Dosage Reduction):
Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence (see **DOSAGE AND ADMINISTRATION**).

Use in Patients With Concomitant Illness:
Clinical experience with lamotrigine in patients with concomitant illness is limited. Caution is advised when using lamotrigine in patients with diseases or conditions that could affect metabolism or elimination of the drug, such as renal, hepatic, or cardiac functional impairment.
Hepatic metabolism to the glucuronide followed by renal excretion is the principal route of elimination of lamotrigine (see **CLINICAL PHARMACOLOGY**).
A study in individuals with severe chronic renal failure (mean creatinine clearance = 13 mL/min) not receiving other AEDs indicated that the elimination half-life of unchanged lamotrigine is prolonged relative to individuals with normal renal function. Until adequate

numbers of patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine, it should be used with caution in these patients, generally using a reduced maintenance dose for patients with significant impairment.
Because there is limited experience with the use of lamotrigine in patients with impaired liver function, the use in such patientsmay be associated with as yet unrecognized risks (see **CLINICAL PHARMACOLOGY**and **DOSAGE AND ADMINISTRATION**).

Binding in the Eye and Other Melanin-Containing Tissues:
Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown.
Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Information for Patients
Prior to initiation of treatment with lamotrigine, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately. In addition, the patient should notify his or her physician if worsening of seizure control occurs.
Patients should be advised that lamotrigine may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on lamotrigine to gauge whether or not it adversely affects their mental and/or motor performance.
Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.
Women should be advised to notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives (including the "pill-free" week) may significantly increase lamotrigine plasma levels (see **PRECAUTIONS**: **Drug Interactions**). Women should also be advised to promptly notify their physician if they experience adverse events or changes in menstrual pattern (e.g., break-through bleeding) while receiving lamotrigine in combination with these medications.
Patients should be advised to notify their physician if they stop taking lamotrigine for any reason and not to resume lamotrigine without consulting their physician.
Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking lamotrigine. See **PATIENT INFORMATION** at the end of this labeling for the text of the leaflet provided for patients.

Laboratory Tests
The value of monitoring plasma concentrations of lamotrigine has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs including AEDs being taken concomitantly (see **Table 3**), monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other anti-seizure drugs and whether or not dosage adjustments are necessary.

Drug Interactions
The net effects of drug interactions with lamotrigine are summarized in Table 3 (see also **DOSAGE AND ADMINISTRATION**).

Oral Contraceptives:
In 16 female volunteers, an oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with a mean decrease in AUC of 52% and in Cmax of 39%. In this study, trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher on average at the end of the week of the inactive preparation compared to trough lamotrigine concentrations at the end of the active hormone cycle.

Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase) occurred during the week of inactive hormone preparation ("pill-free" week) for women not also taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). The increase in lamotrigine plasma levels will be greater if the dose of lamotrigine is increased in the few days before or during the "pill-free" week. Increases in lamotrigine plasma levels could result in dose-dependent adverse effects (see **PRECAUTIONS**: **Concomitant Use With Oral Contraceptives**).

In the same study, co-administration of lamotrigine (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive preparation. There was a mean decrease in the AUC and Cmax of the levonorgestrel component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-pituitary-ovarian axis.

The effects of doses of lamotrigine other than 300 mg/day have not been studied in clinical trials.

The clinical significance of the observed hormonal changes on ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern (e.g., break-through bleeding).

Dosage adjustments will be necessary for most women receiving estrogen-containing oral contraceptive preparations (see **DOSAGE AND ADMINISTRATION**: **Special Populations, Women and Oral Contraceptives**).

Other Hormonal Contraceptives or Hormone Replacement Therapy:
The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine in the presence of progestogens alone will likely not be needed.

Bupropion:
The pharmacokinetics of a 100 mg single dose of lamotrigine in healthy volunteers (n = 12) were not changed by co-administration of bupropion sustained-release formulation (150 mg twice a day) starting 11 days before lamotrigine.

Carbamazepine:
Lamotrigine has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine (see **ADVERSE REACTIONS**).The mechanism of this interaction is unclear.

The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

Felbamate:
In a study of 21 healthy volunteers, co-administration of felbamate (1,200 mg twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Folate Inhibitors:
Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Gabapentin:
Based on a retrospective analysis of plasma levels in 34 patients who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Levetiracetam:
Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

Lithium:
The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by co-administration of lamotrigine (100 mg/day) for 6 days.

Olanzapine:
The AUC and Cmax of olanzapine were similar following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 16) compared to the AUC and Cmax in healthy male volunteers receiving olanzapine alone (n = 16).

In the same study, the AUC and Cmax of lamotrigine was reduced on average by 24% and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers compared to those receiving lamotrigine alone. This reduction in lamotrigine plasma concentrations is not expected to be clinically relevant.

Oxcarbazepine:
The AUC and Cmax of oxcarbazepine and its active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 13) compared to healthy male volunteers receiving oxcarbazepine alone (n = 13).

In the same study, the AUC and Cmax of lamotrigine were similar following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine in healthy male volunteers compared to those receiving lamotrigine alone. Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with co-administration of lamotrigine and oxcarbazepine compared to lamotrigine alone or oxcarbazepine alone.

Phenobarbital, Primidone:
The addition of phenobarbital or primidone decreases lamotrigine steady-state concentrations by approximately 40%.

Phenytoin:
Lamotrigine has no appreciable effect on steady-state phenytoin plasma concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 40%.

Pregabalin:
Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.

Rifampin:
In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25 mg dose of lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

Topiramate:
Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

Valproate:
When lamotrigine was administered to healthy volunteers (n = 18) receiving valproate, the trough steady-state valproate plasma concentrations decreased by an average of 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing therapy did not cause a change in valproate plasma concentrations in either adult or pediatric patients in controlled clinical trials.

The addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 mg/day and 500 mg/day and did not increase as the valproate dose was further increased.

Zonisamide:
In a study of 18 patients with epilepsy, co-administration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day) for 35 days had no significant effect on the pharmacokinetics of lamotrigine.

Known Inducers or Inhibitors of Glucuronidation:
Drugs other than those listed above have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine, and doses of lamotrigine may require adjustment based on clinical response.

Other:
Results of *in vitro* experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone (see **CLINICAL PHARMACOLOGY**: **Pharmacokinetics and Drug Metabolism**). Results of *in vitro* experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6 (see **CLINICAL PHARMACOLOGY**).

Table 3. Summary of Drug Interactions With Lamotrigine

Drug	Drug Plasma Concentration With Adjunctive lamotrigine [*]	Lamotrigine Plasma Concentration With Adjunctive Drugs[†]
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)[‡]	↔[§]	↓
Bupropion	Not assessed	↔

Carbamazepine (CBZ)	↔	↓
CBZ epoxide[¶]	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[#]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[Þ]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔[ß]	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔
↔ = No significant effect.		

***** From adjunctive clinical trials and volunteer studies.
†Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.
‡The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials and the effect may not be similar to that seen with the ethinylestradiol/ levonorgestrel combinations.
§Modest decrease in levonorgestrel (see **PRECAUTIONS**: **Drug Interactions**, **Effect of Lamotrigine on *Oral Contraceptives***).
¶Not administered, but an active metabolite of carbamazepine.
#Slight decrease, not expected to be clinically relevant.
ÞNot administered, but an active metabolite of oxcarbazepine.
ß Slight increase not expected to be clinically relevant.

Drug/Laboratory Test Interactions:
None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for rats, doses that are equivalent to 90 mg/ m2 and 60 to 90 mg/m2, respectively).
Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as 19 mcg/mL have been recorded.
Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the *in vitro* mammalian mouse lymphoma assay). In 2 cytogenetic assays (the *in vitro* human lymphocyte assay and the *in vivo* rat bone marrow assay), lamotrigine did not increase the incidence of structural or numerical chromosomal abnormalities.
No evidence of impairment of fertility was detected in rats given oral doses of lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg per day or 0.4 times the human dose on a mg/m2 basis. The effect of lamotrigine on human fertility is unknown.

Pregnancy:

Teratogenic Effects:

Pregnancy Category C.
No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m2 basis, the highest usual human

maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased.

A behavioral teratology study was conducted in rats dosed during the period of organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg per day or higher displayed a significantly longer latent period for open field exploration and a lower frequency of rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion was increased in offspring of dams receiving 25 mg/kg per day. These doses represent 0.1 and 0.5 times the clinical dose on a mg/m2 basis, respectively.

Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to 0.4 times the highest usual human maintenance dose on a mg/m2 basis.

When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m2 basis) during the latter part of gestation (days 15 to 20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group). Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between day 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

Although lamotrigine was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and wellcontrolled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects:
As with other antiepileptic drugs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Exposure Registry:
To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians should encourage patients to register, before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known, in the American Antiepileptic Drug Pregnancy Registry by calling 1-888-233-2334 (toll free).

Labor and Delivery:
The effect of lamotrigine on labor and delivery in humans is unknown.

Use in Nursing Mothers:
Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breast-feeding while taking lamotrigine is not recommended.

Pediatric Use:
Lamotrigine tablets are indicated as adjunctive therapy for partial seizures, for the generalized seizures of Lennox-Gastaut syndrome in patients above 2 years of age.
Safety and effectiveness in patients below the age of 18 years with Bipolar Disorder has not been established.

Geriatric Use:
Clinical studies of lamotrigine for epilepsy and in Bipolar Disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
SERIOUS RASH REQUIRING HOSPITALIZATION AND DISCONTINUATION OF LAMOTRIGINE, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH THERAPY WITH LAMOTRIGINE. RARE DEATHS HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE (see BOX WARNING).

Epilepsy:

Most Common Adverse Events in All Clinical Studies:

Adjunctive Therapy in Adults With Epilepsy:
The most commonly observed (≥ 5%) adverse experiences seen in association with lamotrigine during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate (see **WARNINGS**).

Approximately 11% of the 3,378 adult patients who received lamotrigine as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%).

In a dose response study in adults, the rate of discontinuation of lamotrigine for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose related.

Monotherapy in Adults With Epilepsy:
The most commonly observed (≥ 5%) adverse experiences seen in association with the use of lamotrigine during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥ 5%) adverse experiences associated with the use of lamotrigine during the conversion to the monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

Approximately 10% of the 420 adult patients who received lamotrigine as monotherapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Epilepsy:
The most commonly observed (≥ 5%) adverse experiences seen in association with the use of lamotrigine as adjunctive treatment in pediatric patients and not seen at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

In 339 patients age 2 to 16 years, with partial seizures or generalized seizures of Lennox-Gastaut syndrome, 4.2% of patients on lamotrigine and 2.9% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with lamotrigine and deterioration of seizure control for patients treated with placebo.

Approximately 11.5% of the 1,081 pediatric patients who received lamotrigine as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

Incidence in Controlled Clinical Studies of Epilepsy:
The prescriber should be aware that the figures in Tables 4, 5, 6, and 7 cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Incidence in Controlled Adjunctive Clinical Studies in Adults With Epilepsy:
Table 4 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy treated with lamotrigine in placebo-controlled trials and were numerically more common in the patients treated with lamotrigine. In these studies, either lamotrigine or placebo was added to the patient’s current AED therapy. Adverse events were usually mild to moderate in intensity.

Table 4. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy* (Events in at least 2% of patients treated with lamotrigine and numerically more frequent than in the placebo group.)

Body System/ Adverse Experience†	Percent of Patients Receiving Adjunctive Lamotrigine (n = 711)	Percent of Patients Receiving Adjunctive Placebo (n = 419)
Body as a whole		
Headache	29	19
Flu syndrome	7	6
Fever	6	4
Abdominal pain	5	4
Neck pain	2	1
Reaction aggravated (seizure exacerbation)	2	1
Digestive		
Nausea	19	10
Vomiting	9	4
Diarrhea	6	4
Dyspepsia	5	2
Constipation	4	3
Tooth disorder	3	2
Anorexia	2	1

Musculoskeletal		
Arthralgia	2	0
Nervous		
Dizziness	38	13
Ataxia	22	6
Somnolence	14	7
Incoordination	6	2
Insomnia	6	2
Tremor	4	1
Depression	4	3
Anxiety	4	3
Convulsion	3	1
Irritability	3	2
Speech disorder	3	0
Concentration disturbance	2	1
Respiratory		

Rhinitis	14	9
Pharyngitis	10	9
Cough increased	8	6
Skin and appendages		
Rash	10	5
Pruritus	3	2
Special senses		
Diplopia	28	7
Blurred vision	16	5
Vision abnormality	3	1
Urogenital		
Female patients only	(n = 365)	(n = 207)
Dysmenorrhea	7	6
Vaginitis	4	1
Amenorrhea	2	1

*Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to lamotrigine or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.
†Adverse experiences reported by at least 2% of patients treated with lamotrigine are included

In a randomized, parallel study comparing placebo and 300 and 500 mg/day of lamotrigine, some of the more common drug-related adverse events were dose related (see **Table 5**).

Table 5. Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial in Adults With Epilepsy

Adverse Experience	Percent of Patients Experiencing Adverse Experiences		
	Placebo (n = 73)	Lamotrigine 300 mg (n = 71)	Lamotrigine 500 mg (n = 72)
Ataxia	10	10	28*†
Blurred vision	10	11	25*†
Diplopia	8	24*	49*†
Dizziness	27	31	54*†
Nausea	11	18	25*
Vomiting	4	11	18*

*Significantly greater than placebo group ($p<0.05$).
†Significantly greater than group receiving lamotrigine 300 mg ($p<0.05$).

Other events that occurred in more than 1% of patients but equally or more frequently in the placebo group included: asthenia, back pain, chest pain, flatulence, menstrual disorder, myalgia, paresthesia, respiratory disorder, and urinary tract infection.

The overall adverse experience profile for lamotrigine was similar between females and males, and was independent of age. Because the largest non-Caucasian racial subgroup was only 6% of patients exposed to lamotrigine in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experience reports by race. Generally, females receiving either adjunctive lamotrigine or placebo were more likely to report adverse experiences than males. The only adverse experience for which the reports on lamotrigine were greater than 10% more frequent in females than males (without a corresponding difference by gender on placebo) was dizziness (difference = 16.5%). There was little difference between females and males in the rates of discontinuation of lamotrigine for individual adverse experiences.

Incidence in a Controlled Monotherapy Trial in Adults with Partial Seizures:
Table 6 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with epilepsy treated with monotherapy with lamotrigine in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

Table 6. Treatment-Emergent Adverse Event Incidence in Adults With Partial Seizures in a Controlled Monotherapy Trial[*] (Events in at least 5% of patients treated with lamotrigine and numerically more frequent than in the valproate group.)

Body System/ Adverse Experience [†]	Percent of Patients Receiving Lamotrigine Monotherapy[‡] (n = 43)	Percent of Patients Receiving Low-Dose Valproate[§] Monotherapy (n = 44)
Body as a whole		
Pain	5	0
Infection	5	2
Chest pain	5	2
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Metabolic and nutritional		
Weight decrease	5	2
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2

Respiratory		
Rhinitis	7	2
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

*****Patients in these studies were converted to lamotrigine or valproate monotherapy from adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.
†Adverse experiences reported by at least 5% of patients are included
‡Up to 500 mg/day.
§1,000 mg/day.

Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients receiving lamotrigine and numerically more frequent than placebo were:

Body as a Whole: Asthenia, fever.

Digestive: Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.

Metabolic and Nutritional: Peripheral edema.

Nervous System: Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased reflexes, nystagmus, irritability, suicidal ideation.

Respiratory: Epistaxis, bronchitis, dyspnea.

Skin and Appendages: Contact dermatitis, dry skin, sweating.

Special Senses: Vision abnormality.

Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy:
Table 7 lists adverse events that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received lamotrigine up to 15 mg/kg per day or a maximum of 750 mg per day. Reported adverse events were classified using COSTART terminology.

Table 7. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients treated with lamotrigine and numerically more frequent than in the placebo group.)

Body System/ Adverse Experience	Percent of Patients Receiving Lamotrigine (n = 168)	Percent of Patients Receiving Placebo (n = 171)
Body as a whole		
Infection	20	17

Fever	15	14
Accidental injury	14	12
Abdominal pain	10	5
Asthenia	8	4
Flu syndrome	7	6
Pain	5	4
Facial edema	2	1
Photosensitivity	2	0
Cardiovascular		
Hemorrhage	2	1
Digestive		
Vomiting	20	16
Diarrhea	11	9
Nausea	10	2
Constipation	4	2
Dyspepsia	2	1
Tooth disorder	2	1

Hemic and lymphatic		
Lymphadenopathy	2	1
Metabolic and nutritional		
Edema	2	0
Nervous system		
Somnolence	17	15
Dizziness	14	4
Ataxia	11	3
Tremor	10	1
Emotional lability	4	2
Gait abnormality	4	2
Thinking abnormality	3	2
Convulsions	2	1
Nervousness	2	1
Vertigo	2	1
Respiratory		

Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Bronchospasm	2	1
Skin		
Rash	14	12
Eczema	2	1
Pruritus	2	1
Special senses		
Diplopia	5	1
Blurred vision	4	1
Ear disorder	2	1
Visual abnormality	2	0
Urogenital		
Male and female patients		

Urinary tract infection	3	0
Male patients only	n = 93	n = 92
Penis disorder	2	0

Bipolar Disorder:

The most commonly observed (≥ 5%) adverse experiences seen in association with the use of lamotrigine as monotherapy (100 to 400 mg/day) in Bipolar Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically more frequent than in placebo-treated patients are included in Table 8. Adverse events that occurred in at least 5% of patients and were numerically more common during the dose escalation phase of lamotrigine in these trials (when patients may have been receiving concomitant medications) compared to the monotherapy phase were: headache (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received lamotrigine (100 to 400 mg/day), 16% of 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued therapy because of an adverse experience. The adverse events which most commonly led to discontinuation of lamotrigine were rash (3%) and mania/hypomania/mixed mood adverse events (2%). Approximately 16% of 2,401 patients who received lamotrigine (50 to 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood adverse events (2%).

Incidence in Controlled Clinical Studies of Lamotrigine for the Maintenance Treatment of Bipolar I Disorder:

Table 8 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with Bipolar Disorder treated with lamotrigine monotherapy (100 to 400 mg/day), following the discontinuation of other psychotropic drugs, in 2 doubleblind, placebo-controlled trials of 18 months' duration and were numerically more frequent than in the placebo group.

Table 8. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder* (Events in at least 5% of patients treated with lamotrigine monotherapy and numerically more frequent than in the placebo group.)

Body System/ Adverse Experience†	Percent of Patients Receiving Lamotrigine n = 227	Percent of Patients Receiving Placebo n = 190
General		
Back pain	8	6
Fatigue	8	5
Abdominal pain	6	3
Digestive		
Nausea	14	11

Constipation	5	2
Vomiting	5	2
Nervous System		
Insomnia	10	6
Somnolence	9	7
Xerostomia (dry mouth)	6	4
Respiratory		
Rhinitis	7	4
Exacerbation of cough	5	3
Pharyngitis	5	4
Skin		
Rash (nonserious) ‡	7	5

*****Patients in these studies were converted to lamotrigine (100 to 400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.
†Adverse experiences reported by at least 5% of patients are included.
‡In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received lamotrigine as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received lamotrigine as adjunctive therapy (see **WARNINGS**).

These adverse events were usually mild to moderate in intensity.

Other events that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients receiving lamotrigine and numerically more frequent than placebo were:

General: Fever, neck pain.

Cardiovascular: Migraine.

Digestive: Flatulence.

Metabolic and Nutritional: Weight gain, edema.

Musculoskeletal: Arthralgia, myalgia.

Nervous System: Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality hypoesthesia.

Respiratory: Sinusitis.

Urogenital: Urinary frequency.

Adverse Events Following Abrupt Discontinuation:
In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse events in Bipolar Disorder patients after abruptly terminating lamotrigine therapy. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients (see **DOSAGE AND ADMINISTRATION**).

Mania/Hypomania/Mixed Episodes:
During the double-blind, placebo-controlled clinical trials in Bipolar I Disorder in which patients were converted to lamotrigine monotherapy (100 to 400 mg/day) from other psychotropic medications and followed for durations up to 18 months, the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5% for patients treated with lamotrigine (n = 227), 4% for patients treated with lithium (n =166), and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined, adverse events of mania (including hypomania and mixed mood episodes) were reported in 5% of patients treated with lamotrigine (n= 956), 3% of patients treated with lithium (n = 280), and 4% of patients treated with placebo (n = 803).

The overall adverse event profile for lamotrigine was similar between females and males, between elderly and nonelderly patients, and among racial groups.

Other Adverse Events Observed During All Clinical Trials for Pediatric and Adult Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders:
Lamotrigine has been administered to 6,694 individuals for whom complete adverse event data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to lamotrigine who experienced an event of the type cited on at least one occasion while receiving lamotrigine. All reported events are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1,000 patients; *rare* adverse events are those occurring in fewer than 1/1,000 patients.

Body as a Whole:
Infrequent: Allergic reaction, chills, halitosis, and malaise.

Rare: Abdomen enlarged, abscess, and suicide/suicide attempt.

Cardiovascular System:
Infrequent: Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation.

Rare: Angina pectoris, atrial fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction.

Dermatological:
Infrequent: Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria. ***Rare:*** Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, seborrhea, Stevens-Johnson syndrome, and vesiculobullous rash.

Digestive System:
Infrequent*:* Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration.

Rare: Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, thirst, and tongue edema.

Endocrine System:
Rare: Goiter and hypothyroidism.

Hematologic and Lymphatic System:
Infrequent: Ecchymosis and leukopenia.

Rare: Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

Metabolic and Nutritional Disorders:
Infrequent: Aspartate transaminase increased.

Rare: Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

Musculoskeletal System:
Infrequent: Arthritis, leg cramps, myasthenia, and twitching.

Rare: Bursitis, joint disorder, muscle atrophy, pathological fracture, and tendinous contracture.

Nervous System:
Frequent: Confusion and paresthesia.

Infrequent: Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, and suicidal ideation.

Rare: Cerebellar syndrome, cerebrovascular accident, cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis.

Respiratory System:
Infrequent: Yawn.

Rare: Hiccup and hyperventilation.

Special Senses:
Frequent: Amblyopia.

Infrequent: Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus.

Rare: Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect.

Urogenital System:
Infrequent: Abnormal ejaculation, breast pain, hematuria, impotence, menorrhagia, polyuria, urinary incontinence, and urine abnormality.

Rare: Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and vaginal moniliasis.

Postmarketing and Other Experience
In addition to the adverse experiences reported during clinical testing of lamotrigine, the following adverse experiences have been reported in patients receiving marketed lamotrigine and from worldwide noncontrolled investigational use. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.
Blood and Lymphatic: Agranulocytosis, aplastic anemia, disseminated intravascular coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.
Gastrointestinal: Esophagitis.
Hepatobiliary Tract and Pancreas: Pancreatitis.
Immunologic: Lupus-like reaction, vasculitis.
Lower Respiratory: Apnea.
Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.
Neurology: Exacerbation of parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics.
Non-site Specific: Hypersensitivity reaction, multiorgan failure, progressive immunosuppression.

DRUG ABUSE AND DEPENDENCE
The abuse and dependence potential of lamotrigine have not been evaluated in human studies.

OVERDOSAGE

Human Overdose Experience:
Overdoses involving quantities up to 15 g have been reported for lamotrigine, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

Management of Overdose:
There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed (see **CLINICAL PHARMACOLOGY**). It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of lamotrigine.

DOSAGE AND ADMINISTRATION

Epilepsy:

Adjunctive Use:
Lamotrigine tablets are indicated as adjunctive therapy for partial seizures and the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients (≥ 2 years of age).

Monotherapy Use:
Lamotrigine tablets are indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

Safety and effectiveness of lamotrigine tablets have not been established (1) as initial monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs.

Bipolar Disorder:
Lamotrigine tablets are indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of lamotrigine tablets in the acute treatment of mood episodes has not been established.

General Dosing Considerations for Epilepsy and Bipolar Disorder Patients:
The risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose escalation of lamotrigine tablets is exceeded. There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) coadministration of lamotrigine tablets with valproate, (2) exceeding the recommended initial dose of lamotrigine tablets, or (3) exceeding the recommended dose escalation for lamotrigine tablets. However, cases have been reported in the absence of these factors (see **BOX WARNING**). Therefore, it is important that the dosing recommendations be followed closely.
It is recommended that lamotrigine not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine, unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued

lamotrigine, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the previous dose, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued lamotrigine for a period of more than 5 halflives, it is recommended that initial dosing recommendations and guidelines be followed.

Lamotrigine Added to Drugs Known to Induce or Inhibit Glucuronidation:
Drugs other than those listed in **PRECAUTIONS**: **Drug Interactions**have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine, and doses of lamotrigine may require adjustment based on clinical response.

Target Plasma Levels for Patients With Epilepsy or Bipolar Disorder:
A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of lamotrigine should be based on therapeutic response.

The half-life of lamotrigine is affected by other concomitant medications (see **CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism**).

See also **DOSAGE AND ADMINISTRATION: Special Populations.**

Special Populations:

Women and Oral Contraceptives:

Starting Lamotrigine in Women Taking Oral Contraceptives:
Although estrogen-containing oral contraceptives have been shown to increase the clearance of lamotrigine (see **PRECAUTIONS**: **Drug Interactions**), no adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of estrogen-containing oral contraceptives. Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive therapy with lamotrigine based on the concomitant AED (see **Table 11**). See below for adjustments to maintenance doses of lamotrigine in women taking estrogen-containing oral contraceptives.

Adjustments to the Maintenance Dose of Lamotrigine:
(1) Taking Estrogen-Containing Oral Contraceptives: For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of lamotrigine will in most cases need to be increased, by as much as 2-fold over the recommended target maintenance dosein order to maintain a consistent lamotrigine plasma level (see **PRECAUTIONS**: **Drug Interactions**). ***(2) Starting Estrogen-Containing Oral Contraceptives:*** In women taking a stable dose of lamotrigine and not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose will in most cases need to be increased by as much as 2-fold, in order to maintain a consistent lamotrigine plasma level. The dose increases should begin at the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100 mg/day every week. Dose increases should not exceed the recommended rate unless lamotrigineplasma levels or clinical response support larger increases (see **Table 11**, **column 2**).Gradual transient increases in lamotrigine plasma levels may occur during the week of inactive hormonal preparation ("pill-free" week), and these increases will be greater if dose increases are made in the days before or during the week of inactive hormonal preparation. Increased lamotrigine plasma levels could result in additional adverse events, such as dizziness, ataxia, and diplopia (see **PRECAUTIONS**: **Drug Interactions**). If adverse events attributable to lamotrigine consistently occur during the "pill-free" week, dose adjustments to the overall maintenance dose may be necessary. Dose adjustments limited to the "pill-free" week are not recommended. For women taking lamotrigine in addition to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment should be necessary to the dose of lamotrigine. ***(3) Stopping Estrogen-Containing Oral Contraceptives:*** For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of lamotrigine will in most cases need to be decreased by as much as 50%, in order to maintain a consistent lamotrigine plasma level. The decrease in dose of lamotrigine should not exceed 25% of the total daily dose per week over a 2-week period, unless clinical response or lamotrigine plasma levels indicate otherwise (see **PRECAUTIONS**: **Drug Interactions**). For women taking lamotrigine in addition to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment to the dose of lamotrigine should be necessary.

Women and Other Hormonal Contraceptive Preparations or Hormone Replacement Therapy:
The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine in the presence of progestogens alone will likely not be needed.

Patients With Hepatic Impairment:
Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe liver dysfunction (see **CLINICAL PHARMACOLOGY**), the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

Patients With Renal Functional Impairment:
Initial doses of lamotrigine should be based on patients' AED regimen (see above); reduced maintenance doses may be effective for patients with significant renal functional impairment (see **CLINICAL PHARMACOLOGY**). Few patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine. Because there is inadequate experience in this population, lamotrigine should be used with caution in these patients.

Epilepsy:

Adjunctive Therapy With Lamotrigine for Epilepsy:
This section provides specific dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of age. Within each of these age groups, specific dosing recommendations are provided depending upon concomitant AED (Table 9 for patients 2 to 12 years of age and Table 11 for patients greater than 12 years of age). A weight based dosing guide for pediatric patients on concomitant valproate is provided in Table 10.

Patients 2 to 12 Years of Age:
Recommended dosing guidelines are summarized in Table 9. Note that some of the starting doses and dose escalations listed in Table 9 are different than those used in clinical trials; however, the maintenance doses are the same as in clinical trials. Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestions that the risk of rash may be decreased by smaller starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg, regardless of age or concomitant AED, may need to be increased as much as 50%, based on clinical response.

Table 9. Escalation Regimen for Lamotrigine in Patients 2 to 12 Years of Age With Epilepsy

	For Patients Taking Valproate (see Table 10 for weight-based dosing guide)	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate
Weeks 1 and 2	**0.15 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 10 for weight-based dosing guide).	**0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet.	**0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet.
Weeks 3 and 4	**0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 10 for weight-based dosing guide).	**0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet.	**1.2 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet.
Weeks 5 onwards to maintenance	The dose should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	The dose should be increased every 1 to 2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the	The dose should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily

		previously administered daily dose	dose
Usual Maintenance Dose	**1 to 5 mg/kg/day** (maximum 200 mg/day in 1 or 2 divided doses). **1 to 3 mg/kg/day** with valproate alone	**4.5 to 7.5 mg/kg/day** (maximum 300 mg/day in 2 divided doses)	**5 to 15 mg/kg/day** (maximum 400 mg/day in 2 divided doses)
Maintenance dose in patients less than 30 kg	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response

Note: Only whole tablets should be used for dosing

*****Rifampin and estrogen-containing contraceptives have also been shown to increase the apparent clearance of lamotrigine (see **PRECAUTIONS: Drug Interactions**).

Table 10. The Initial Weight-Based Dosing Guide for Patients 2 to 12 Years Taking Valproate (Weeks 1 to 4) With Epilepsy

If the patient's weight is		Give this daily dose, using the most appropriate combination of lamotrigine 2-mg and 5-mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every *other* day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day

Patients Over 12 Years of Age:
Recommended dosing guidelines are summarized in Table 11

Table 11. Escalation Regimen for Lamotrigine in Patients Over 12 Years of Age With Epilepsy

	For Patients Taking Valproate	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate

Weeks 1 and 2	**25 mg every *other* day**	**25 mg every day**	**50 mg/day**
Weeks 3 and 4	**25 mg every day**	**50 mg/day**	**100 mg/day** (in 2 divided doses)
Weeks 5 onwards to maintenance	Increase by 25 to 50 mg/day every 1 to 2 weeks	Increase by 50 mg/day every 1 to 2 weeks	Increase by 100 mg/day every 1 to 2 weeks.
Usual Maintenance Dose	**100 to 400 mg/day** (1 or 2 divided doses) **100 to 200 mg/daywith valproate alone**	**225 to 375 mg/day** (in 2 divided doses).	**300 to 500 mg/day** (in 2 divided doses).

*****Rifampin and estrogen-containing oral contraceptives have also been shown to increase the apparent clearance of lamotrigine (see **PRECAUTIONS**: **Drug Interactions**)

Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate as the Single AED to Monotherapy With Lamotrigine in Patients ≥ 16 Years of Age With Epilepsy:
The goal of the transition regimen is to effect the conversion to monotherapy with lamotrigine under conditions that ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid titration of lamotrigine.

The recommended maintenance dose of lamotrigine as monotherapy is 500 mg/day given in 2 divided doses.

To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of lamotrigine should not be exceeded (see **BOX WARNING**).

Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin, Phenobarbital, or Primidone to Monotherapy With Lamotrigine:
After achieving a dose of 500 mg/day of lamotrigine according to **Table 11**, the concomitant AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant AED is based on experience gained in the controlled monotherapy clinical trial.

Conversion From Adjunctive Therapy With Valproate to Monotherapy With Lamotrigine:
The conversion regimen involves 4 steps. (see **Table 12)**.

Table 12. Conversion From Adjunctive Therapy With Valproate to Monotherapy With Lamotrigine in Patients ≥16 Years of Age With Epilepsy

	Lamotrigine	Valproate
Step 1	Achieve a dose of 200 mg/day according to guidelines in Table 11 (if not already on 200 mg/day).	Maintain previous stable dose.
Step 2	Maintain at 200 mg/day.	Decrease to 500 mg/day by decrements no greater than 500 mg/day per week and then maintain the dose of 500 mg/day for 1 week.

Step 3	Increase to 300 mg/day and maintain for 1 week.	Simultaneously decrease to 250 mg/day and maintain for 1 week.
Step 4	Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day.	Discontinue.

Conversion From Adjunctive Therapy With Antiepileptic Drugs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy With Lamotrigine:
No specific dosing guidelines can be provided for conversion to monotherapy with lamotrigine with AEDs other than carbamazepine, phenobarbital, phenytoin, primidone, or valproate.

Usual Maintenance Dose for Epilepsy:
The usual maintenance doses identified in Tables 9 -11 are derived from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of lamotrigine was established. In patients receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital, or primidone **without valproate**, maintenance doses of adjunctive lamotrigine as high as 700 mg/day have been used. In patients receiving **valproate alone**, maintenance doses of adjunctive lamotrigine as high as 200 mg/ day have been used. The advantage of using doses above those recommended in the Tables 9 -12 has not been established in controlled trials.

Discontinuation Strategy for Patients With Epilepsy:
For patients receiving lamotrigine in combination with other AEDs, a reevaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse experiences is observed.

If a decision is made to discontinue therapy with lamotrigine, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal (see **PRECAUTIONS**).

Discontinuing carbamazepine, phenytoin, phenobarbital, or primidone should prolong the half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.

Bipolar Disorder:
The goal of maintenance treatment with lamotrigine tablets is to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The target dose of lamotrigine tablets is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, which increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated, however, no additional benefit was seen at 400 mg/day compared to 200 mg/day (see **CLINICAL STUDIES**: **Bipolar Disorder**). Accordingly, doses above 200 mg/day are not recommended. Treatment with lamotrigine tablets is introduced, based on concurrent medications, according to the regimen outlined in Table 13. If other psychotropic medications are withdrawn following stabilization, the dose of lamotrigine tablets should be adjusted. For patients discontinuing valproate, the dose of lamotrigine tablets should be doubled over a 2 week period in equal weekly increments (see **Table 14**). For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the dose of lamotrigine tablets should remain constant for the first week and then should be decreased by half over a 2 week period in equal weekly decrements (see **Table 14**). The dose of lamotrigine tablets may then be further adjusted to the target dose (200 mg) as clinically indicated.
Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking lamotrigine (see **DOSAGE AND ADMINISTRATION, Special Populations, Women and oral contraceptives, Adjustments to the maintenance dose of lamotrigine**).
If other drugs are subsequently introduced, the dose of lamotrigine tablets may need to be adjusted. In particular, the introduction of valproate requires reduction in the dose of lamotrigine tablets (see **CLINICAL PHARMACOLOGY**: **Drug Interactions**).
To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of lamotrigine tablets should not be exceeded (see **BOX WARNING**).

Table 13. Escalation Regimen for Lamotrigine for Patients With Bipolar Disorder*

	For Patients Not Taking Carbamazepine, (or Other Enzyme-Inducing Drugs†) or Valproate‡	For Patients Taking Valproate‡	For Patients Taking Carbamazepine (or Other Enzyme-Inducing Drugs) and Not Taking Valproate‡

Weeks 1 and 2	25 mg daily	25 mg every *other* day	50 mg daily
Weeks 3 and 4	50 mg daily	25 mg daily	100 mg daily, in divided doses
Week 5	100 mg daily	50 mg daily	200 mg daily, in divided doses
Week 6	200 mg daily	100 mg daily	300 mg daily, in divided doses
Week 7	200 mg daily	100 mg daily	up to 400 mg daily, in divided doses

*****See **CLINICAL PHARMACOLOGY**, ***Drug Interactions*** and **PRECAUTIONS**, **Drug Interactions** for a description of known drug interactions.
†Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to increase the apparent clearance of lamotrigine.
‡Valproate has been shown to decrease the apparent clearance of lamotrigine.

Table 14. Adjustments to Lamotrigine Dosing for Patients With Bipolar Disorder Following Discontinuation of Psychotropic Medications*

	Discontinuation of Psychotropic Drugs (excluding Carbamazepine, or Other Enzyme-Inducing Drugs)†	After Discontinuation of Valproate‡	After Discontinuation of Carbamazepine, or Other Enzyme-Inducing Drugs†
		Current lamotrigine dose (mg/day) 100	Current lamotrigine dose (mg/day) 400
Week 1	Maintain current Lamotrigine dose	150	400
Week 2	Maintain current Lamotrigine dose	200	300
Week 3 onward	Maintain current Lamotrigine dose	200	200

*****See **CLINICAL PHARMACOLOGY**, ***Drug Interactions***and **PRECAUTIONS**, **Drug Interactions** for a description of known drug interactions
† Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to increase the apparent clearance of lamotrigine.
‡Valproate has been shown to decrease the apparent clearance of lamotrigine.

There is no body of evidence available to answer the question of how long the patient should remain on lamotrigine tablet therapy. Systematic evaluation of the efficacy of lamotrigine in patients with either depression or mania who responded to standard therapy during an acute 8 to 16 week treatment phase and were then randomized to lamotrigine or placebo for up to 76 weeks of observation for affective relapse demonstrated a benefit of such maintenance treatment (see **CLINICAL STUDIES**: **Bipolar Disorder**). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation Strategy in Bipolar Disorder:
As with other AEDs, lamotrigine tablets should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the incidence, type, or severity of adverse experiences following abrupt termination of lamotrigine. In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Discontinuation of lamotrigine tablets should involve a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) unless safety concerns require a more rapid withdrawal.

HOW SUPPLIED:
Lamotrigine tablets, 25 mg are light yellow, round, flat, bevel edged, uncoated tablets, embossed “RDY” on one side and “220” on other side with bisect line and are supplied in:

Boxes of 10x10 UD 100 NDC 63739-448-10

Lamotrigine tablets, 100 mg are light yellow, round, flat, bevel edged, uncoated tablets, embossed “RDY” on one side and “221” on other side with bisect line.
Lamotrigine tablets, 150 mg are light yellow, round, flat, bevel edged, uncoated tablets, embossed “RDY” on one side and “222” on other side with bisect line .
Lamotrigine tablets, 200 mg are light yellow, round, flat, bevel edged, uncoated tablets, embossed “RDY” on one side and “223” on other side with bisect line.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.
Manufactured By:
Dr. Reddy’s Laboratories Limited
Bachepalli-502 325, INDIA
Distributed By:
McKesson Packaging
Concord, NC 28027
Revised: 09/08
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PATIENT INFORMATION
The following wording is contained in a separate leaflet provided for patients.
Information for the Patient
Lamotrigine Tablets

25 mg, light yellow, round, embossed “RDY” on one side and “220” on other side with bisect line	**100 mg, light yellow, round, embossed “RDY” on one side and “221” on other side with bisect line**	**150 mg, light yellow, round, embossed “RDY” on one side and “222” on other side with bisect line**	**200 mg, light yellow, round, embossed “RDY” on one side and “223” on other side with bisect line**

NOTE: The above wording describes the color and embossing that is on each strength of lamotrigine tablets. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these wordings to make sure you have received the correct medicine.
Please read this leaflet carefully before you take lamotrigine and read the leaflet provided with any refill, in case any information has changed.
This leaflet provides a summary of the information about your medicine. Please do not throw away this leaflet until you have finished your medicine. This leaflet does not contain all the information about lamotrigine and is not meant to take the place of talking with your doctor. If you have any questions about lamotrigine, ask your doctor or pharmacist.
Information About Your Medicine:
The name of your medicine is lamotrigine. The decision to use lamotrigine is one that you and your doctor should make together. When taking lamotrigine, it is important to follow your doctor’s instructions.
1. The Purpose of Your Medicine:
For Patients With Epilepsy: Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people aged 2 years or older.
For Patients With Bipolar Disorder: Lamotrigine is used as maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes in people aged 18 years or older treated for acute mood episodes with standard therapy.
If you are taking lamotrigine to help prevent extreme mood swings, you may not experience the full effect for several weeks. Occasionally, the symptoms of depression or bipolar disorder may include thoughts of harming yourself or committing suicide. Tell your doctor immediately or go to the nearest hospital if you have any distressing thoughts or experiences during this initial period or at any other time.
Also contact your doctor if you experience any worsening of your condition or develop other new symptoms at any time during your treatment.
Some medicines used to treat depression have been associated with suicidal thoughts and suicidal behavior in children or teenagers. Lamotrigine is not approved for treating children or teenagers with mood disorders such as bipolar disorder or depression.
2. Who Should Not Take Lamotrigine:
You should not take lamotrigine if you had an allergic reaction to it in the past.
3. Side Effects to Watch for:
- Most people who take lamotrigine tolerate it well. Common side effects with lamotrigine include dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, insomnia, and rash. Lamotrigine may cause other side effects

not listed in this leaflet. If you develop any side effects or symptoms you are concerned about or need more information, call your doctor.

- Although most patients who develop rash while receiving lamotrigine have mild to moderate symptoms, some individuals may develop a serious skin reaction that requires hospitalization. Rarely, deaths have been reported. These serious skin reactions are most likely to happen within the first 8 weeks of treatment with lamotrigine. Serious skin reactions occur more often in children than in adults.

- Rashes may be more likely to occur if you: (1) take lamotrigine in combination with valproate [valproic acid, or divalproex sodium], (2) take a higher starting dose of lamotrigine than your doctor prescribed, or (3) increase your dose of lamotrigine faster than prescribed.

- It is not possible to predict whether a mild rash will develop into a more serious reaction. **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. A doctor should evaluate your condition and decide if you should continue taking lamotrigine.**

4. The Use of Lamotrigine During Pregnancy and Breast-feeding:
The effects of lamotrigine during pregnancy are not known at this time. If you are pregnant or are planning to become pregnant, talk to your doctor. Some lamotrigine passes into breast milk and the effects of this on infants are unknown. Therefore, if you are breast-feeding, you should discuss this with your doctor to determine if you should continue to take lamotrigine.

5. Use of Birth Control Pills or Other Female Hormonal Products:

- Do not start or stop using birth control pills or other female hormonal products until you have consulted your doctor. Stopping or starting these products may cause side effects (such as dizziness, lack of coordination, or double vision) or decrease the effectiveness of lamotrigine.

- Tell your doctor as soon as possible if you experience side effects or changes in your menstrual pattern (e.g., break-through bleeding) while taking lamotrigine and birth control pills or other female hormonal products.

6. How to Use Lamotrigine:

- It is important to take lamotrigine exactly as instructed by your doctor. The dose of lamotrigine must be increased slowly. It may take several weeks or months before your final dosage can be determined by your doctor, based on your response.

- Do not increase your dose of lamotrigine or take more frequent doses than those indicated by your doctor. Contact your doctor, if you stop taking lamotrigine for any reason. Do not restart without consulting your doctor.

- If you miss a dose of lamotrigine, do not double your next dose.

- Always tell your doctor and pharmacist if you are taking any other prescription or over-the-counter medicines. Tell your doctor before you start any other medicines.

- Do NOT stop taking lamotrigine or any of your other medicines unless instructed by your doctor.

- Use caution before driving a car or operating complex, hazardous machinery until you know if lamotrigine affects your ability to perform these tasks.

- If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types of seizures.

7. How to Take Lamotrigine:
Lamotrigine tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.

8. Storing Your Medicine:
Store lamotrigine at room temperature away from heat and light. Always keep your medicines out of the reach of children.
This medicine was prescribed for your use only to treat seizures or to treat Bipolar Disorder. Do not give the drug to others.
If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.
Rx only
Manufactured by
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA
Distributed By:
McKesson Packaging
Concord, NC 28027

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PACKAGE DISPLAY PANEL

LABEL TEXT
NDC 63739-448-10
Lamotrigine
Tablets, 25mg
UD 100 Tablets (10x10)
Rx Only
EACH SCORED TABLET CONTAINS:
25 mg of lamotrigine
See package insert for Dosage and Administration.
DISPENSE in a tight, light-resistant container as defined in the USP.
STORE at 25° C (77° F) excursions permitted to 15-30° C (59-86° F)
[see USP Controlled Room Temperature] in a dry place.
Mfg. By: Dr. Reddy's Laboratories Limited
Bachepalli-502 325, INDIA
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